Study NM14161

This was a Phase III randomized, multicenter (17), double-blind, double-dummy, placebo-controlled U.S. study. The study consisted of three periods: (1) a 4-week single-blind placebo lead-in period, (2) a 52-week double-blind treatment period of placebo, 60 mg orlistat tid, or 120 mg orlistat tid, and (3) an additional 52-week double-blind treatment period with patients continued on the same regimen as during the first year. To quality for period 1 the patient had to meet the entry criteria. To qualify for period 2 and randomization the patient had to complete period 1 and achieve ≥75% dosing compliance. To participate in period 3, the patient had to complete period 2 and achieve ≥75% dosing compliance. In the first 2 periods patients were on a mildly hypocaloric diet and in period 3 an eucaloric diet.

Study Objectives
From the study protocol, the objectives of the study were:
1. To determine the long-term weight control effect of 120 mg orlistat tid, 60 mg orlistat tid, or placebo tid in combination with dietary counseling for 2 years in the primary care setting.
2. To determine the weight loss effect of the three treatments in combination with a hypocaloric diet during the first year of treatment.
3. To determine the long-term tolerability of orlistat, 120 mg tid or 60 mg tid with meals to obese patients.

Rationale for Dosage Selection
In a 12-week Phase II dose finding study the 120 mg tid dose showed a significantly greater effect on weight loss than placebo and the 60 mg tid dose showed a trend toward weight loss. In the pharmacology studies, the 60 mg dose was associated with substantially increased fecal fat. To fully assess the 60 mg tid dose, it was included in this study. The 120 mg tid and 60 mg tid dosages were compared to placebo to determine the long term weight control effect of orlistat after 104 weeks of treatment.

Primary Efficacy Variable and Hypothesis
The primary efficacy measurement was the change from baseline in body weight at weeks 56 and 108. The weight change at weeks 28 and 80 are also of interest. The null hypothesis was that the mean weight change in patients on the placebo, 60 mg orlistat, and 120 mg orlistat treated groups is the same after 104 weeks of double-blind treatment. The same type of hypothesis was also tested at weeks 28, 56, and 80.

Treatment Assignment
The study included men or nonpregnant women 18 years or older with a body mass index (BMI) ≥30 kg/m$^2$ and ≤43 kg/m$^2$. Patients who completed the single-blind lead-in period, had been at least 75% compliant with the dosing regimen, and had vitamin levels which were not below the reference range on two consecutive samples taken during the lead-in were randomized to 120 mg orlistat, 60 mg orlistat, or placebo. Patients were stratified by weight loss during the placebo lead-in period which integrates the compliance of diet, motivation, and initial body size into a measure of potential success in weight loss. Patients who lost 2.0 kg or less during the lead-in were in stratum one and those who lost more than 2.0 kg were in stratum two. Thus, the treatment groups were balanced in terms of potential success with diet alone.

Patient Disposition
A total of 796 patients at 17 centers in the United States entered the placebo lead-in period. Of the 642 patients who completed the lead-in period, 214 patients each were randomized to receive 60 mg orlistat tid, 120 mg orlistat tid, and placebo.

The number of patients who completed one year of treatment was 122 (57%), 154 (72%), and 151 (71%), in the placebo, 60 mg and 120 groups, respectively, and the number of patients who completed two years was 91(43%), 120 (56%), and 117 (55%), respectively, for the 3 treatment groups.

Seven of the randomized patients were excluded from the intent-to-treat population which had 212 patients, 213 patients and 210 patients in the placebo, 60 mg, and 120 mg groups, respectively.



Patient Withdrawals
During the first year of double-blind treatment, 96 (45%) patients in the placebo, 62 (29%) in the 60 mg and 64 (30%) in the 120 mg groups discontinued prematurely. Throughout the two-year double-blind treatment, 58% of the placebo, 44% of the 60 mg, and 45% of the 120 mg patients withdrew prematurely. Table 26 displays a summary of the year one withdrawals.

Table 26. Summary of Premature Withdrawal During the First Year

| Reasons | Placebo (n=214) n | % | 60 mg (n=214) n | % | 120 mg (n=214) n | % |
|---|---|---|---|---|---|---|
| Lost to follow-up | 34 | (15.9%) | 16 | (7.5%) | 26 | (12.1%) |
| Administrative | 29 | (13.6%) | 13 | (6.1%) | 10 | ( 4.7%) |
| Adverse event | 12 | ( 5.6%) | 10 | (4.7%) | 15 | ( 7.0%) |
| Treatment failure | 5 | ( 2.3%) | 6 | (2.8%) | 2 | ( 0.9%) |
| Refused treatment | 3 | ( 1.4%) | 4 | (1.9%) | 1 | ( 0.5%) |
| Died during study | | 0 | 0 | | 1 | ( 0.5%) |
| Did not cooperate | 7 | ( 3.3%) | 6 | (2.8%) | 5 | ( 2.3%) |
| Protocol violation | 6 | ( 2.8%) | 7 | (3.3%) | 4 | ( 1.9%) |

A total of 97 patients withdrew in the 120 mg group, 23 (24%) with adverse events. The 60 mg group and placebo group had 15% (14/94) and 12% (15/123), withdrew respectively, due to adverse events.

Demographic Characteristics

The majority of patients were white (577/635,91%), female (497/635, 78.3%) with an average age of 42.5 years, a weight of 100.9 kg and a BMI of 36 kg/m$^2$. The three treatment groups were similar in these demographic characteristics.



Efficacy Results

Primary Analysis

The sponsor performed an analysis of covariance using weight loss during the placebo lead-in as a covariate. There was a statistically significant difference in weight loss between the two orlistat groups and placebo ($p<0.001$); however a center-by-treatment interaction ($p=0.134$) was observed for the ITT population. After examining the least squares mean for each center, the placebo patients in center 12322 were losing more weight than the orlistat groups and in center 12327 the 60 mg orlistat gained weight while placebo lost weight. The sponsor indicated that center 12327 had the lowest completion rate (24%, 9/37) among all 17 centers with large number of noncompliant patients who discontinued either voluntarily or by the investigator. After excluding center 12327, the interaction was no longer significant ($p>0.4$). The sponsor also indicated that the least squares mean differences from placebo were very similar with or without center 12327.

This reviewer performed analysis of variance on the outcomes of change of weight (kg) from baseline with treatment, center, stratum and all 3 interaction terms in the model. At year one for the ITT population with the last observations carried forward, the overall p-value was statistically significant ($p=0.0001$). The treatment-by-center and the treatment-by-stratum interactions were significant ($p=0.1$). Among the three pairwise comparisons, both 120 mg versus placebo and 60 mg versus placebo were statistically significant with $p=0.0001$ but the 120 mg

versus 60 mg comparison was not statistically significant with p=0.1375. The analysis on weight change from baseline to year two results were similar to the year one results with an overall significant difference (p=0.0001). There was no significant difference between 120mg and 60 mg groups (p=0.57). The baseline weight and the least squares mean of change of weight from baseline by stratum are displayed in Table 27.

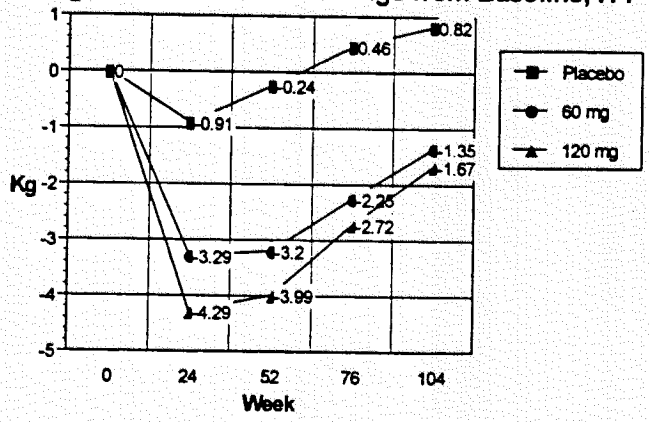
Table 27. Baseline Weight and Year One Weight Change from Baseline

| | Stratum 1 | | Stratum 2 | | **Overall** | |
|---|---|---|---|---|---|---|
| | n | Baseline | n | Baseline | **n** | **Baseline** |
| Placebo | 85 | 98.5 Kg | 127 | 99.5 Kg | **212** | **99.1 Kg** |
| Orlistat | | | | | | |
| 60 mg | 92 | 97.3 Kg | 121 | 98.4 Kg | **213** | **97.9 Kg** |
| 120 mg | 90 | 97.7 Kg | 120 | 98.2 Kg | **210** | **98.0 Kg** |

| | Stratum 1 | | Stratum 2 | | **Overall** | |
|---|---|---|---|---|---|---|
| | Change from Baseline | (Difference from Placebo) | Change from Baseline | (Difference from Placebo) | **Change from Baseline** | **(Difference from Placebo)** |
| Year 1 | | | | | | |
| Placebo | +0.27 | | -0.76 | | **-0.24** | |
| 60 mg | -1.63 | (-1.90) | -4.77 | (-4.02) | **-3.20** | **(-2.96)** |
| 120 mg | -3.18 | (-3.45) | -4.81 | (-4.05) | **-3.99** | **(-3.75)** |
| Year 2 | | | | | | |
| Placebo | +0.92 | | +0.72 | | **+0.82** | |
| 60 mg | -0.87 | (-1.79) | -1.83 | (-2.55) | **-1.35** | **(-2.17)** |
| 120 mg | -1.53 | (-2.46) | -1.82 | (-2.54) | **-1.67** | **(-2.50)** |

Figure 12 is the LSM change from baseline of the four time points.

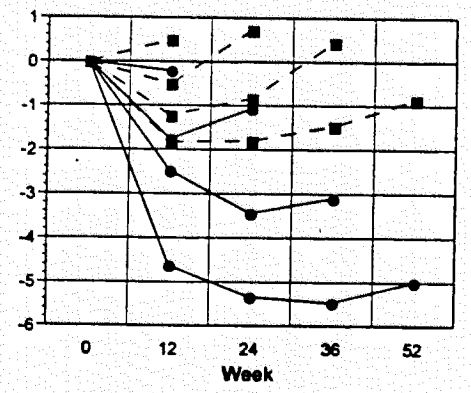
**Fig. 12 NM14161-LSM Change from Baseline, ITT**




The mean change from baseline in weight loss in cohort of patients with last observation at week 12, 24, 36, and 52 is displayed in Figures 13.

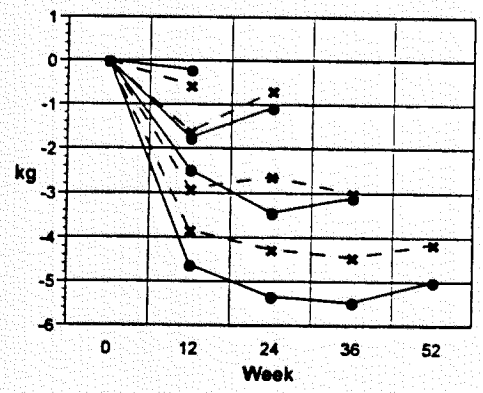
**Fig. 13 Mean Weight Change from Baseline of 4 Patient Cohorts, Year 1**

**NM14161-Mean Change from Baseline of Patient Cohort by Treatment (120 mg Orlistat vs Placebo)**




| | | | | | |
|---|---|---|---|---|---|
| ■ Placebo | n | 16 | 28 | 23 | 132 |
| ● 120 mg | n | 16 | 16 | 16 | 156 |

**NM14161-Mean Change from Baseline of Patient Cohort by Treatment (120 mg vs 60 mg Orlistat)**




| | | | | | |
|---|---|---|---|---|---|
| ✱ 60 mg | n | 18 | 13 | 19 | 159 |
| ● 120 mg | n | 16 | 16 | 16 | 156 |

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Responders Analysis

At year one, percentages of patients who lost ≥5% from baseline weight were compared among the three treatment groups. The overall p-value is 0.001. The pairwise comparisons showed that the 120 mg and 60 mg groups were both better than placebo with $p<0.001$ and $p=0.001$, respectively. The 120 mg-60 mg comparison was not statistically significant ($p=0.1$). The 10% responder analysis results were similar to the 5% responder analysis

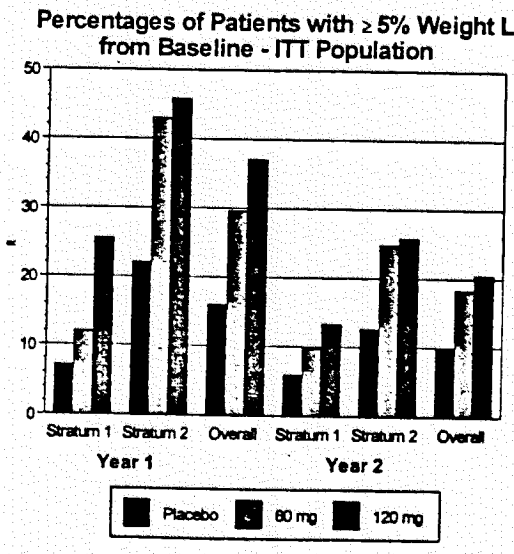
results. The following 2 tables display the percentages of responders by stratum for year 1 and year 2.

Table 28. Percentage of 5% responders by Stratum - ITT Population

| | Year 1 | | | Year 2 | | |
|---|---|---|---|---|---|---|
| | Placebo | 60 mg | 120 mg | Placebo | 60 mg | 120 mg |
| Stratum 1 (lead-in≤2Kg) | 7.1% (6/85) | 12.0% (11/92) | 25.6% (23/90) | 5.9% (5/85) | 9.8% (9/92) | 13.3% (12/90) |
| Stratum 2 (lead-in>2Kg) | 22.1% (28/127) | 43.0% (52/121) | 45.8% (55/120) | 12.6% (16/127) | 24.8% (30/121) | 25.8% (31/120) |
| **Overall** | **16.0% (34/212)** | **29.6% (63/213)** | **37.1% (78/210)** | **9.9% (21/212)** | **18.3% (39/213)** | **20.5% (43/210)** |



**Fig. 14 Percentages of Patients with ≥5% and ≥10% Weight Loss**



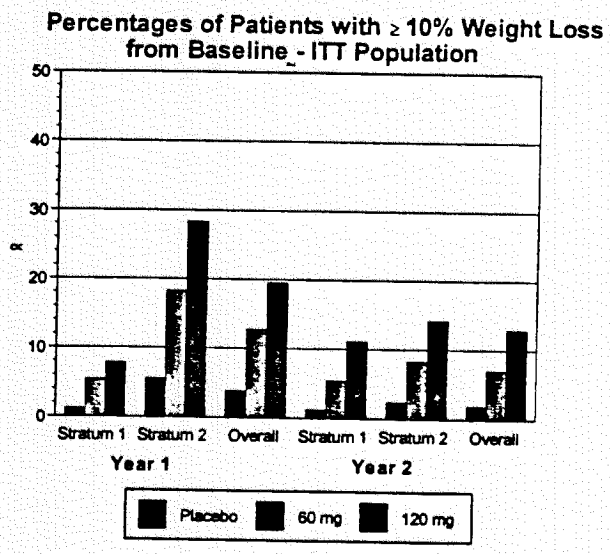




Table 29. Percentage of 10% responders by Stratum - ITT Population

| | Year 1 | | | Year 2 | | |
|---|---|---|---|---|---|---|
| | Placebo | 60 mg | 120 mg | Placebo | 60 mg | 120 mg |
| Stratum 1 (lead-in≤2Kg) | 1.2% (1/85) | 5.4% (5/92) | 7.8% (7/90) | 1.2% (1/85) | 5.4% (5/92) | 11.1% (10/90) |
| Stratum 2 (lead-in>2Kg) | 5.5% (7/127) | 18.2% (22/121) | 28.3% (34/120) | 2.4% (3/127) | 8.3% (10/121) | 14.2% (17/120) |
| **Overall** | **3.8% (8/212)** | **12.7% (27/213)** | **19.5% (41/210)** | **1.9% (4/212)** | **7.0% (15/213)** | **12.9% (27/210)** |

Serum Lipids

At the end of week 52, the total cholesterol and LDL cholesterol in the placebo group increased by 4.4% and 6.8%, respectively. For orlistat 60 mg group the mean increases were 0.96% and 1.35%, respectively. For orlistat 120 mg group the changes from baseline were -0.51% and -1.63%, respectively. The HDL cholesterol was increased in all three treatment groups with the greatest increase observed in the placebo group (8.6%) compared to 5.5% in the 60 mg orlistat and 6.1% in the 120 mg orlistat. The least squares mean percent change in serum lipids are displayed in Table 30.

Table 30. LSM % Change from Baseline of Serum Lipids

| | | | LSMean %Change from Baseline (p-value) | |
|---|---|---|---|---|
| | n | Baseline | Week 52 | Week 104 |
| Total | | | | |
| Placebo | 195 | 5.02 | 4.17 | 5.09 |
| 60 mg | 201 | 5.01 | 0.24 (0.001) | 2.19 (0.018) |
| 120 mg | 201 | 4.99 | -0.32 (0.000) | 3.84 (0.306) |
| LDL | | | | |
| Placebo | 195 | 3.17 | 6.15 | 6.73 |
| 60 mg | 201 | 3.11 | 0.27 (0.001) | 2.78 (0.027) |
| 120 mg | 201 | 3.16 | -1.76 (0.000) | 2.23 (0.012) |
| HDL | | | | |
| Placebo | 195 | 1.17 | 8.55 | 8.44 |
| 60 mg | 201 | 1.22 | 4.97 (0.022) | 5.85 (0.121) |
| 120 mg | 201 | 1.20 | 6.42 (0.170) | 7.43 (0.544) |
| Triglycerides | | | | |
| Placebo | 195 | 1.66 | 2.59 | 6.32 |
| 60 mg | 201 | 1.65 | 1.91 (0.841) | 7.18 (0.832) |
| 120 mg | 201 | 1.55 | 2.80 (0.945) | 11.38 (0.208) |

Adverse Events

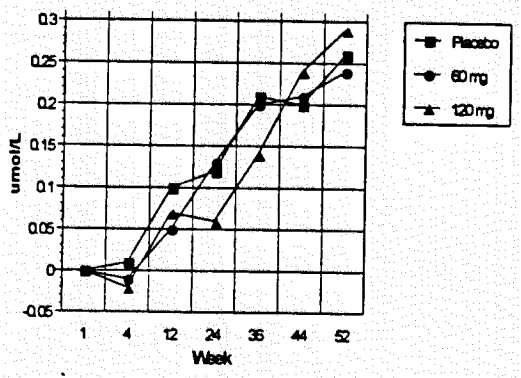
The largest between-group difference in adverse events rate is in the gastrointestinal system. The event rates of 76.2% (160/210) 120 mg orlistat patients, 70.9% (151/213) 60 mg orlistat patients and 53.8% (114/212) placebo patients was statistically significant (p=0.001).

Plasma Vitamin Levels
The observed data of the safety population (same as ITT) at year one is displayed in the following figures.

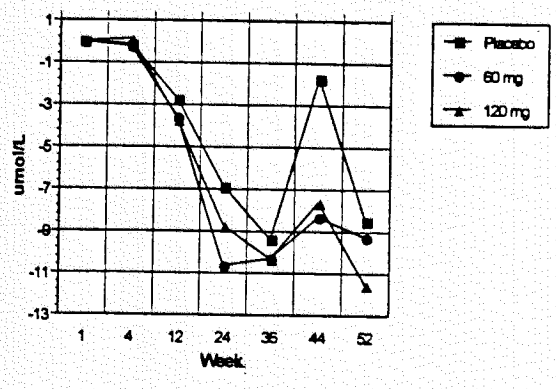
**Fig. 15 Year One Serum Vitamin Levels**



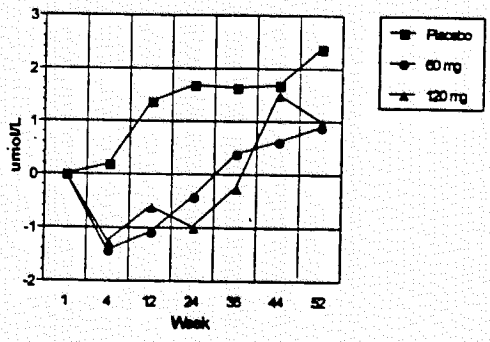
Mean Change of Vitamin A - Year One



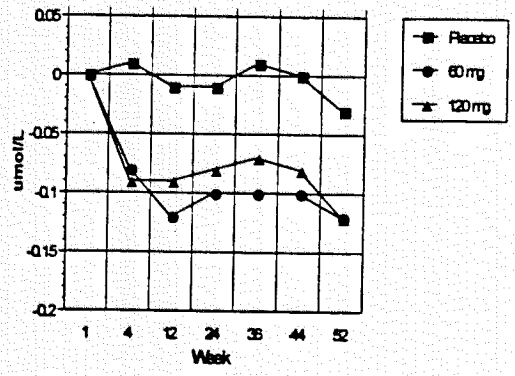

Mean Change of Vitamin D - Year One




Mean Change of Vitamin E - Year One




Mean Change of Beta-Caractene - Year One



The least squares mean change in vitamins at end of 52 weeks of treatment is displayed in Table 29.

Table 29. LSM Change in Levels of Vitamin, Year One

| umole/L | n | Baseline | LSMean Change from Baseline (difference from placebo) | p-value |
|---|---|---|---|---|
| Vitamin A | | | | |
| Placebo | 207 | 1.80 | 0.19 | |
| | 210 | 1.79 | 0.17 (-0.02) | 0.550 |
| 60 mg | 205 | 1.78 | 0.23 ( 0.04) | 0.305 |
| 120 mg | | | | |
| Vitamin D | | | | |
| Placebo | 207 | 64.76 | -5.77 | |
| 60 mg | 210 | 67.32 | -6.60 (-0.84) | 0.674 |
| 120 mg | 205 | 62.48 | -11.39 (-5.62) | 0.005 |
| Vitamin E | | | | |
| Placebo | 207 | 24.44 | 1.75 | |
| 60 mg | 210 | 24.63 | 0.75 (-0.99) | 0.044 |
| 120 mg | 205 | 24.08 | 0.92 (-0.83) | 0.095 |
| Beta Carotene | | | | |
| Placebo | 207 | 0.32 | -0.44 | |
| 60 mg | 210 | 0.35 | -0.09 (-0.05) | 0.004 |
| 120 mg | 205 | 0.32 | -0.09 (-0.05) | 0.001 |

Subgroup Analysis in Gender, Race, and Age



There is no treatment-by-gender interaction (p=0.7). The least squares mean weight change by gender and the difference from placebo is as follows:

Table 30. Subgroup Analysis of Gender

| | Male | | Female | |
|---|---|---|---|---|
| | n | LSM (diff) | n | LSM (diff) |
| Year 1 Placebo | 47 | +0.43 | 165 | -0.60 |
| 60 mg | 47 | -2.60 (-3.03) | 166 | -3.66 (-3.06) |
| 120 mg | 44 | -4.00 (-4.42) | 166 | -4.07 (-3.47) |
| Year 2 Placebo | 47 | +2.31 | 165 | +0.54 |
| 60 mg | 47 | -0.77 (-3.08) | 166 | -1.38 (-1.92) |
| 120 mg | 44 | -0.35 (-2.67) | 166 | -1.83 (-2.37) |

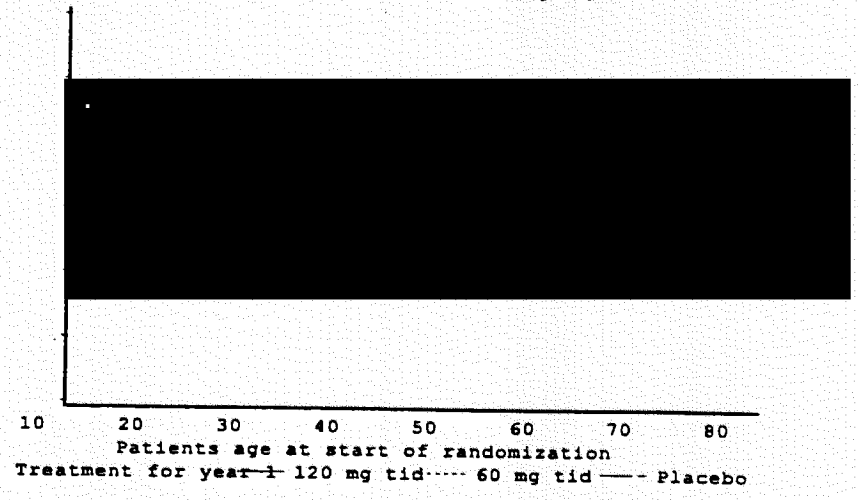
The LSM weight lost by race is as follows:

Table 31. Subgroup Analysis of Race

| | | White | | | Black | | |
|---|---|---|---|---|---|---|---|
| | | n | LSM | (diff) | n | LSM | (diff) |
| Year 1 | Placebo | 193 | -0.51 | | 15 | +0.92 | |
| | 60 mg | 200 | -3.46 | (-2.96) | 9 | -0.38 | (-1.30) |
| | 120 mg | 184 | -4.30 | (-3.80) | 19 | -2.35 | (-3.27) |
| Year 2 | Placebo | 193 | +0.87 | | 15 | +1.59 | |
| | 60 mg | 200 | -1.30 | (-2.18) | 9 | +1.38 | (-0.22) |
| | 120 mg | 184 | -1.56 | (-2.43) | 19 | -1.31 | (-2.90) |

An analysis of covariance with age as a covariate was performed. The end of year one results showed a significant treatment effect (p=0.022) and significant treatment-by-age interaction (p=0.005). The interaction was caused by the negative slope (-0.13) of the 120 mg group and a positive slope (0.03) of the 60 mg and placebo (0.01) groups. The older patients in 120 mg group lost more weight than the younger patients. The following figure displays the regression lines.

**Fig. 16 Weight Loss at Year One by Age**

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Patients were stratified by age (<45 or ≥45 years old). The treatment-by-age interaction was significant (p=0.0007, year 1 and p=0.07, year 2). The LSM by age is displayed in Table 32.

Table 32. Mean Weight Change at Year One by Age

| | | Age<45 | | | Age≥45 | | |
|---|---|---|---|---|---|---|---|
| | | n | LSM | (diff) | n | LSM | (diff) |
| Year 1 | Placebo | 134 | -0.55 | | 78 | -0.08 | |
| | 60 mg | 129 | -3.98 | (-3.43) | 84 | -2.58 | (-2.49) |
| | 120 mg | 118 | -2.93 | (-2.38) | 92 | -5.51 | (-5.43) |
| Year 2 | Placebo | 134 | +0.66 | | 78 | +1.38 | |
| | 60 mg | 129 | -1.63 | (-2.30) | 84 | -0.66 | (-2.04) |
| | 120 mg | 118 | -0.90 | (-1.56) | 92 | -2.33 | (-3.71) |

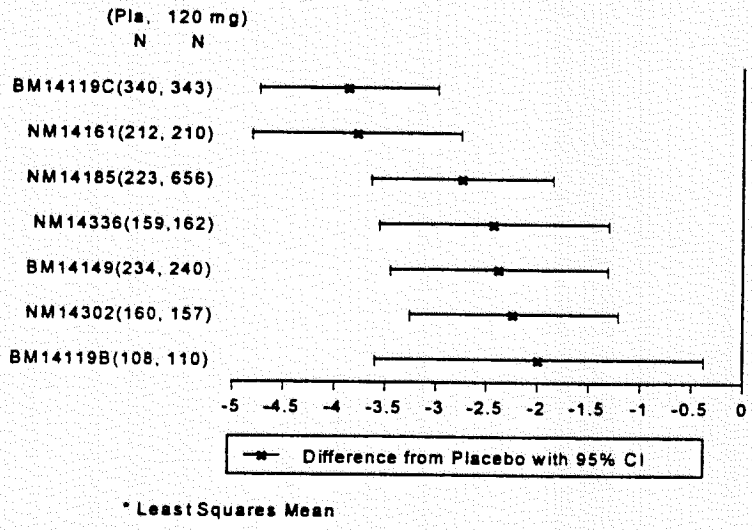
Conclusions of Study NM14161

The year one ITT population with last observation carried forward analysis of variance showed that the orlistat 60 mg and 120 mg tid group had a mean weight loss of 3.2 Kg and 4.0 Kg, respectively, compared to a 0.2 Kg weight loss in the placebo group. This was statistically significant (p=0.0001). The mean difference from placebo is 3.0 Kg (C.I. 1.9, 4.0) for the 60 mg group and 3.8 Kg (C.I. 2.7, 4.8) for the 120 mg group. On the responder analysis of the percentage of patients who lost 5% or more from baseline, the difference from placebo was ~14%(C.I. 6%, 21%) and ~21%(C.I. 13%, 29%) for the 60 mg and 120 mg groups, respectively.

Overall Summary of Efficacy

The difference between 120 mg tid orlistat and placebo for the mean change from baseline to year one in weight (kg) by study is displayed in figure 17 and the difference in percentage of patients who lost at least 5% weight from baseline weight to year one is displayed in figure 18.

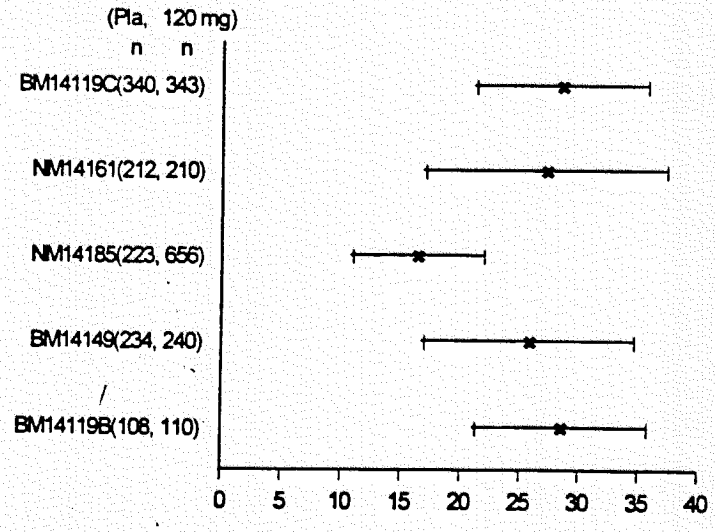
**Fig 17. Treatment Difference in Change of Weight from Baseline*, Orlistat 120 mg tid vs. Placebo at One Year - ITT (LOCF)**




* Least Squares Mean



**Fig. 18. Treatment Difference between Orlistat 120 mg and Placebo at One Year, Percentage of Patients with ≥5% Weight Loss, ITT (LOCF)**



Overall Conclusion [redacted]

The studies were consistent in that they showed that orlistat 120 mg tid is statistically significantly different from placebo in weight loss from baseline to 52 weeks. The orlistat 120 mg tid patients lost 2 kg to 4 kg more than placebo patients among the studies in the intent-to-treat population with last observation carried forward data. The difference between orlistat 120 mg tid and placebo in the percentage of patients who lost at least 5% from baseline weight ranged from 16% to 28%. The adverse events in gastrointestinal symptoms are significantly higher in the orlistat 120 mg group than in the placebo group. There were small but statistically significant changes in both serum lipids and vitamins. The serum lipids were improved in the orlistat 120 mg group in total cholesterol and LDL cholesterol but not in triglyceride. The HDL increased more in the placebo group. Serum level in vitamin D and E and β-carotene were less in orlistat treatment patients than placebo patients after one year but vitamin A was not significantly different from placebo.

/S/ [redacted]
Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello /S/ [redacted]

Dr. Nevius /S/ [redacted] 4-30-97

cc: Arch NDA 20-766
HFD-510
HFD-510/SSobel
HFD-510/GTroendle
HFD-510/EColman
HFD-510/MHess
HFD-715/Division file, DMarticello, LPian
Pian/33510/wpfiles/xenical
This review contains 42 pages

[redacted]

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: APR 29 1997

From: Mathematical Statistician (HFD-715)

Through: Director, Division of Biometrics II (HFD-715) /S/ [redacted]

Subject: Labeling for Xenical

To: File (NDA 20-766) [redacted]

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The weight loss results under Clinical Studies section of the labeling provided the percentages of patients who lost **greater** than 5% and 10% from initial body weight (screening) in Study 14119C. This reviewer used the **at least** 5% and 10% weight loss from baseline (randomization) as the outcome variable and patients who completed week 52 in the analysis the results are as follow:

| | % of Patients Losing ≥5% from **Baseline** Reviewer's | ≥10% from **Baseline** (Sponsor's) |
|---|---|---|
| Completers<br>Xenical (n=281)<br>Placebo (n=259) | 64% (77.2% n=271)<br>32% (57.4% n=249) | 28% (46.9%)<br>10% (21.3%) |
| Intent-to-Treat<br>Xenical (n=340)<br>Placebo (n=343) | 55% (68.5% n=339)<br>27% (49.1% n=337) | 25% (39.0%)<br>8% (17.6%) |

The pooled data analysis from 5 clinical trials suggested by Dr. Colman is valid provided that there is no treatment-by-study interaction. This reviewer performed the analysis and found no treatment-by-study interaction (p=0.7).

The primary efficacy measurement for the first year was change from baseline in body weight at day 365. The weight loss in kilogram should also be described in the label.

/S/ [redacted]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

/S/ [redacted]

Concur: Mr. Marticello

[redacted] BEST POSSIBLE

cc:Archi. NDA 20-766
HFD-510
HFD-510/SSobel, GTroendle, MHess
HFD-510/EColman
HFD-715/Division file, DMarticello, LPian, Chron.

Pian/74257/wpfiles/xenical

[redacted] APPEARS THIS WAY ON ORIGINAL